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# THE CORRELATION OF RABBIT PNEUMONIA AND HUMAN INFLUENZAL PNEUMONIA

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In this paper I wish to report certain studies on pneumonia in rabbits and incidently to compare the lesions with the lesions in human influenzal pneumonia.

An epidemic of rabbit influenza occurred among the laboratory animals in the fall and winter of 1918 and the spring and summer of 1919. While contemporaneous with the epidemic of influenza, there was no reason whatever to surmise a common etiology. It had occurred many times before in the laboratory.

The duration of the disease was variable; most animals succumbed at the end of from 5 to 7 days. Early there was loss of appetite and a thin, watery nasal discharge, accompanied by frequent sneezing. The discharge descended from the nares to the breast and anterior extremities and, as the disease progressed, became mucoid and purulent in character. Animals used for experimental purposes (infections, vaccine injections, etc.) appeared more susceptible and succumbed 6 to 48 hours earlier as a rule.

The exciting cause is the *B. bipolaris*, an organism classed in the hemorrhagic septicemia group. This organism has been reported under various names: e. g., *B. bronchisepticus*, *B. bovissepticus*, *Bacillus of pleuropneumonia*, *Bacillus of rabbit septicemia*, etc. In this article I use the term *B. bipolaris*. It was recovered from the following sources: nasal discharge, nasopharynx, pleural fluid, pericardial fluid and heart blood. Koch's postulates were fulfilled. The bacillus is short, about 1-3 microns in length, staining intensely at the poles and only slightly in the middle, and at times is pleomorphic. It is nonmotile, nonspore-forming, aerobic and facultative anaerobic. It stains with the ordinary aniline dyes and is negative to the Gram stain. In fluid medium the organism is often coccoid while on solid medium it tends to retain its characteristic form. It has appeared in cultures as a coccoid bacillus, a diplobacillus, a streptobacillus and at times in threadlike

forms similar to *B. influenzae*. After cultivation on artificial medium for a few generations, it tends to lose its characteristic bipolar staining.

In the literature are reports of a number of varieties of bacilli isolated from rabbits dying of lung involvement. Beck<sup>1</sup> mentions a small gram-negative, nonmotile bacillus, pathogenic for rabbits, guinea-pigs and mice, having a marked tendency to form threads, as the cause of "Breustseuche" in rabbits. Laven<sup>2</sup> described a bacillus pathogenic for rabbits and guinea-pigs; small, gram-negative, variable in size and a tendency to grow in thread and chain forms. It is strictly hemolytic and gives a peculiar sperm-like odor on blood agar. Kurita<sup>3</sup> described a small gram-negative polar staining bacillus which killed animals when injected by producing "Breustseuche." Undoubtedly the organism isolated from this series of cases belong to the same general group as those above described. It produces a confluent lobular pneumonia on intratracheal insufflation.

Experimental production of the disease was effected as follows: a 24-hour agar slant of bacteria was emulsified in 5 c.c. sterile normal salt solution and sprayed into the nose and nasopharynx of 5 healthy animals. All succumbed to the disease in the acute stages. To prevent the possibility of contamination at the institution, 2 animals, obtained from a source other than that from which they were usually obtained and kept at a distance of some miles from the laboratory, readily contracted and succumbed to the disease 8 days after inoculation.

A series of 17 animals was collected, of which 12 succumbed to the disease acquired in the natural manner and in 5 the disease was produced experimentally. Necropsies were performed within 1 to 14 hours after death. Sections for microscopic study were taken from the lungs, trachea, heart, liver, kidney and spleen, fixed in formalin or Zenker's fluid, sectioned in paraffin and stained with hematoxylin and eosin. In certain instances, special staining methods were also used.

Macroscopically the lungs presented the typical picture of a confluent bronchopneumonia. They did not completely collapse on opening the chest and the pleural surfaces were frequently mottled with patchy areas of dark, bluish red color; often in the acute stage the pleura was covered with a thin layer of fibrin. The pleural cavities usually contained some fluid. Small consolidated masses varying in size from that of a pinpoint to that of a pea, hard and firm, with crepitating lung tissue surrounding them could be felt, usually more prominent in the lower lobes and especially of the right lung. The distribution of the bronchopneumonic areas was as follows: upper lobe, left 12%, right 14%; middle lobe, right 18%; lower lobe, left 26%; right 30%.

On cut section the lungs were moist and edematous, with a red, frothy liquid, sometimes purulent in character, exuding from the cut ends of the bronchioles. On scraping, in some instances, plugs of necrotic material were removed. The distribution of the consolidated areas was variable; in the more

<sup>1</sup> Kolle-Wassermann: Handbuch der path. Mikroorg., 1903, 3, p. 405.

<sup>2</sup> Centralbl. f. Bakteriol., 1, O., 1910, 54, p. 97.

<sup>3</sup> Ibid., 1909, 49, p. 508.

acute cases it was usually in small patches near the periphery of the lung, in the more chronic it often became confluent in character and was situated around a central bronchiole. The consolidated areas were usually surrounded by a zone of hyperemia. At times the centers of these consolidated areas appeared necrotic. Engorgement of all the pulmonary vessels was particularly evident.

Microscopically, the picture varied with the stage of the disease. In the acute stage, perivascular edema and leukocytic infiltration were the most prominent features. In some instances, a clear, edematous exudate containing few or no cells was prominent. In rabbit 6, there was a proliferation of cells beneath the intimal coat of the blood vessels. As the stage of the disease became more advanced, it tended to resemble red hepatization. The alveolar epithelial cells were swollen, edematous and degenerative. In some instances, complete desquamation had taken place. The interstitial tissue was edematous and swollen, the vessels hyperemic and distended, with perivascular infiltration, as a rule. The alveoli were packed with red cells and desquamated alveolar cells together with strands of fibrin interspersed. In the advanced stage, the invasion of large numbers of white cells occurred, similar to gray hepatization. The fibrin increased in amount and later at times became organized. The outlines of the alveoli were indistinct and in some areas imperceptible, the process having become confluent with subsequent obliteration of the individual alveoli. Occasionally the pneumonic process was complicated by a tendency to small abscess formation. In the small consolidated areas, central necrosis, quite intense in some instances, was noted. Not infrequently this process involved over one half of the consolidated area. In many instances the bronchioles contained an exudate, the constituents of which depended on the stage of the process. All stages of cellular degeneration could be observed. Phagocytosis was often seen; the phagocytized structures being red cells, polymorphonuclears and cellular debris. Definite focal hemorrhages were occasionally seen, often involving large areas.

In the acute cases, less alteration was noticed, a slight transudation of serum and a few leukocytes plus slight hyperemia being the chief manifestations. In the more subacute and protracted cases, the picture varied from degenerative changes of the epithelial lining to complete desquamation and necrosis of the underlying tissue. The larger bronchi were less involved, this varying from slight to intense necrosis and sloughing. In most instances the peribronchial lymphatic spaces were distended and infiltrated with leukocytes.

The trachea contained a slimy, mucoid or frothy, slightly blood tinged fluid, especially near the bifurcation. On removal of this material, intense hyperemia of the mucosa was evident. In some instances, on opening the trachea, the affected side revealed more of the frothy, blood tinged fluid showing a fairly sharp line separating the diseased from the normal side. Microscopically an acute tracheitis was present, with edema and marked degenerative changes in the epithelial lining in some instances; in others only a moderate hyperemia was present.

Desquamative bronchiolitis was frequent in places with complete or nearly total destruction of the mucosa. Strands of fibrin and polymorphonuclear cells were found abundantly in some bronchioles; others appeared quite normal.

The heart was little altered. In most cases, a few c.c. of clear, straw-colored fluid was contained within the pericardial sac. In no animal in this series was there evidence of a fibrinous pericarditis. Occasionally the right heart was dilated. The valves were normal in every case except one in which a small vegetation occurred on the mitral valve and endocardium, from which

a mixed culture of hemolytic streptococci and a gram-negative bacillus was obtained. The muscle was reddish brown and without evidence of myocarditis. Microscopically there was no noteworthy change.

The kidneys appeared little altered excepting slight congestion. Microscopically, the glomeruli and tubules showed some evidence of degeneration in many of the animals. In a few, foci of hemorrhages were present. The liver parenchyma was in some instances slightly fatty. No areas of focal necrosis were found. The spleen was acutely swollen, without other noteworthy change.

I wish now to correlate certain features of the rabbit disease with those in the human influenzal lesions. This is done because of the general similarity of the two diseases in their symptomatology and epidemiology and possibly also in their etiology. With reference to etiology it is quite certain that *B. bipolaris* is the cause of the rabbit influenza. A similar organism, the Pfeiffer bacillus, is often associated with human influenza but presumably is only a common secondary invader and not the primary cause. It no doubt often plays a rôle in the causation of influenzal pneumonia and being somewhat similar to *B. bipolaris* it was thought a comparison especially of the pulmonary lesions in these two conditions would be of value.

A comparison of *B. bipolaris* and *B. influenzae* (Pfeiffer bacillus) has already been made by Davis.<sup>4</sup> While similar in many ways certain distinguishing features exist, symbiosis and the hemophilic property being the most important; some other points of difference exist which need not be detailed here. It will be sufficient to state that these organisms cannot be considered identical or even very closely related.

Rabbit bronchopneumonia and human influenzal bronchopneumonia reveal somewhat similar gross alterations if approximately the same stages of the disease are taken. In the former, on opening the pleural cavities, the lungs do not completely collapse and the pleural cavities usually contain a moderate amount of fluid, seldom blood tinged and containing fibrin. The picture in human influenzal bronchopneumonia is an excessive amount of blood tinged fluid, usually remarkably free from fibrin. On the pleural surfaces in both diseases are seen frequently small petechial and confluent hemorrhages. In rabbits the distribution of the consolidated areas is variable; in the acute cases they are for the most part situated in small patches near the periphery of the lung; in the more chronic ones they tend to become confluent and may be located more centrally. In several specimens the centers of these consolidated areas appeared to be necrotic and were studded with

<sup>4</sup> Jour. Infect. Dis., 1913, 12, p. 42.

little yellow pin point size foci which on scraping often yielded plugs of necrotic material. While human influenzal pneumonia presents in the main a similar pathological picture one obvious difference is the lack of the central necrosis in the small consolidated areas and a greater tendency to become confluent, resulting in the massive confluent pseudolobar pneumonia, so called.

Microscopically the rabbit bronchopneumonia shows a more marked perivascular edema and leukocytic infiltration than does the human type. The central necrosis above mentioned is much in evidence in the rabbit lung while little if any mention is made of it in the human disease. The exudative material is perhaps richer in cell content than is the case in human influenzal bronchopneumonia. Fibrin is not especially abundant, simulating therefore the human influenzal bronchopneumonia. Small miliary abscesses are not infrequently found. Focal necrosis of the pulmonary blood vessels was not evident in the rabbits as described by LeCount<sup>5</sup> in human influenzal bronchopneumonia.

In order to compare the pathogenesis of these two infections it will be necessary to discuss experimental pneumonia. There are two principal theories with respect to the initial mode of pneumonic infection, namely, the hematogenous which has received little experimental support, having consistently failed in the hands of Wadsworth,<sup>6</sup> Rasquin<sup>7</sup> and Armstrong,<sup>8</sup> and the bronchiogenic, which has received a certain amount of confirmation in the experimental production of pneumonia in animals by various methods of intratracheal or intra-bronchial insufflation.

Müller<sup>9</sup> undertook a study of the pathogenesis of aspiration pneumonia experimentally produced in rabbits by vagotomy. From his observations he inferred that the bacteria gained entrance into the pulmonary tissue at the point where the cuboidal epithelium of the terminal bronchiole gave place to the flattened epithelium of the alveolar duct and atrium and that the invasion was facilitated by the mechanical injury produced by aspirated foreign material. He established the fact that further spread of the infection was by way of the interstitial tissue of the lung framework and by way of the alveolar walls.

<sup>5</sup> Jour. Amer. Med. Assn., 1919, 72, p. 1519.

<sup>6</sup> Am. J. Med. Sc., 1904, 127, p. 851.

<sup>7</sup> Arch. med. exper. et d'anat. path., 1910, 22, p. 804.

<sup>8</sup> Brit. Med. J., 1914, 2, suppl. 57.

<sup>9</sup> Arch. klin. Med., 1902, 74, p. 80.

Blake and Cecil<sup>10</sup> state that pneumonia was consistently produced in normal monkeys by intratracheal injections of pneumococci and showed that the pneumonia produced ran a clinical course identical with that of man. They furthermore state that attempts to produce pneumonia by subcutaneous or intravenous inoculations have consistently failed and therefore conclude that pneumonia is a bronchiogenic and not a hematogenous affair.

They, however, obtained their experimental results by intratracheal inoculation of the animals through needle puncture. Winternitz, Smith and Robinson<sup>11</sup> have pointed out that in such inoculations, the needle, though sterile on entry, is unquestionably infected when it is withdrawn and consequently a possible path of infection to the lung may be found elsewhere than through the lumen of the trachea. They demonstrated that the submucosa of the trachea and bronchi furnishes a pathway of infection to the lung. It contains a rich plexus of lymphatics prominent everywhere, devoid of valves. There is a continuity throughout this lymphatic system so that bacteria which once find their way into it may easily spread.

In this rabbit bronchopneumonias produced by intratracheal injections through a soft rubber catheter, the process was apparently not bronchiogenic in character, for the patchy, confluent consolidations were not situated near the large bronchi or the hilum of the lung; the larger bronchi in the greater proportion of cases were uninvolved and no evidence of bacterial passage through the mucosa was discernible. The consolidations were situated indiscretely over the lung surface, both near the periphery and the center and often numbering as high as 15 to 20 to a lobe. Microscopically the lymphatics, especially the perivascular, were dilated and infiltrated with leukocytes. Bacteria were not seen in them. From this it seems reasonable to assume that the rabbit bronchopneumonia is a hematogenous or lymphogenous affair in contradistinction to human, influenzal bronchopneumonia. This view is in harmony with the fact that this infection in rabbits often manifests itself as a septicemia, indeed is often called rabbit septicemia.

No direct evidence was obtainable as to the site of the primary invasion. That the bacteria passed through the mucosa somewhere near the hilum of the lung and entered the lymphatic system seems probable for two reasons: first, the catheter was inserted to the

<sup>10</sup> J. Exp. Med., 1920, 31, p. 445.

<sup>11</sup> Bull. Johns Hopkins Hosp., 1920, 31, p. 63.

bifurcation of the trachea and second, the peribronchial lymphatics were involved in most instances.

In no instance have observations been recorded of the tendency to multiple abscess formation in human influenzal bronchopneumonia comparable to the striking process seen in rabbit pneumonia in which the consolidated areas undergo an intense central necrosis without delimitation of the process by capsule formation. Large regional softenings as seen at times in human lungs following pneumonia were not observed in the rabbits.

#### SUMMARY

Rabbit bronchopneumonia may be caused by *B. bipolaris* which belongs in the hemorrhagic septicemia group. The disease may be produced experimentally.

Under natural and experimental conditions a bronchopneumonia appears which is usually distributed throughout all portions of the lung, both peripherally and centrally, the microscopic picture being dependent on the stage of the disease. Peribronchial and perivascular infiltration of the lymph spaces and regions of central necrosis were the most constant lesions.

A comparison of rabbit pneumonia and influenzal pneumonia as described by various writers indicates certain points of similarity, but also certain differences. Grossly and microscopically both are bronchopneumonic processes, often confluent in type. They differ, however, in that in rabbit pneumonia the perivascular and peribronchial leukocytic infiltration of the lymph spaces and the regions of necrosis in the consolidated portions are more constant and striking features. The latter appears to be especially distinctive of rabbit pneumonia.